DOCUMENT RESUME

ED 291 006 CG 020 538

TITLE	Progress Report on Alzheimer's Disease: Volume II.
INSTITUTION	National Inst. on Aging (DHHS/PHS), Bethesda, MD.
REPORT NO	NIH-84-2500
PUB DATE	Jul 84
NOTE	31p.; For volume III, see CG 020 539.
AVAILABLE FROM	Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
PUB TYPE	Reports - General (140)
EDRS PRICE	MF01/PC02 Plus Postage.
DESCRIPTORS	*Behavioral Science Research; *Medical Research; *Mental Disorders; Older Adults; *Research and Development; Research Coordinating Units; *Research Needs; Research Projects; Scientific Research
IDENTIFIERS	*Alzheimers Disease

ABSTRACT

This document provides an overview of the state of scientific study of Alzheimer's disease, a disease of catastrophic proportions whose symptoms include serious forgetfulness; changes in personality; confused, restless, and irritable behavior; and problems with judgment, concentration, writing, reading, speech, and naming of objects. It discusses biological mechanisms related to Alzheimer's disease, including glucose metabolism and the molecular pathology of changes in the proteins of nerve cells of the cerebral cortex which are associated with the disease. Research conducted in the last decade about the cause of Alzheimer's is reviewed, including trace metal, slow virus, immunological, and genetic studies. Psychosocial research is discussed, noting that to date behavioral science research has focused on diagnostic tests to differentiate between Alzheimer's disease and multi-infarct dementia, on changes in language use in relation to brain function and dysfunction, and on special supports needed by families of victims. A review of clinical research discusses sleep studies and treatment approaches. Intramural initiatives by the National Institute on Aging, the National Institutes of Health, the National Institute of Mental Health, and the National Institute for Neurological and Communicative Disorders and Stroke are described. The report concludes that advances have been made in the past decade and that, at some future date, Alzheimer's disease may be prevented or cured. (ABL)

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PROGRESS REPORT ON ALZHEIMER'S DISEASE: Volume II

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service — National Institutes of Health

Executive Summary

Alzheimer's disease, the major form of old age "senility," is the cause of serious confusion and forgetfulness in some 2,000,000 elderly Americans and a probable contributor to the institutionalization of as many has half of the more than one million elderly in long-term care facilities.

Since 1976, when the interest of three Federal research organizations—the National Institute on Aging (NIA), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the National Institute of Mental Health (NIMH)—focused on the prevalence and possible causes of this disorder, government research activities on the dementias of aging have increased by more than 800 percent.

A major inroad came when it was demonstrated that Alzheimer's disease is a brain disorder and not a normal consequence of aging. Since then, some studies have looked at the biological mechanisms of Alzheimer's disease, in particular the role and chemical composition of structures that irreversibly alter aging brain cells and play a major role in the disease.

Other scientists have employed a variety of methods to investigate what causes Alzheimer's disease. Research on certain well-established chemical changes in the Alzheimer brain have become more intriguing recently because of evidence of the selective destruction of cells in a part of the base of the brain which provides these chemicals to higher brain regions. Studies on the contribution of aluminum to the disease's development have been linked with a new environmental hypothesis. Scientists have furthered their understanding of the effects of viral infections on the central nervous system in diseases similar to Alzheimer's disease. Genetic studies have shown a clustering of Alzheimer cases in some families although no consistent pattern of genetic transmission has been demonstrated.

Research is just beginning to address whether psychosocial factors may contribute to the causes or development of Alzheimer's disease. To date, behavioral sciences research has focused mainly on the search for diagnostic tests, on changes in language use, and on special supports needed by families of victims.

On the basis of early findings of biomedical, social, and behavioral studies, a number of scientists are developing projects aimed at improving care and treatment for Alzheimer victims. Clinicians need a more sensitive and reliable diagnostic test or some kind of "marker" which will detect the disorder in its earliest stages. Other clinical researchers are attempting to compensate for established declines in brain chemistry as a way of treating the serious symptoms of Alzheimer's disease. This research is set in the context of major advances in the field of neuroscience, including advances, aided by computer technology, in the ability to view and understand the workings of the living human brain.

The following report provides a brief overview of the state of scientific study of Alzheimer's disease.

Alzheimer's disease is indeed a disease of catastrophic proportions. Now regarded as the major form of old age "senility," it is a surprisingly common disorder that affects the cells of the brain. While experts formerly believed that Alzheimer's disease only occurred in persons under 65, this disorder is now recognized as the most common cause of severe intellectual impairment in older individuals. Whether the classic form of Alzheimer's disease, which was first described in a middle-aged adult, is identical in cause, mechanisms, and course to Alzheimer's disease in old age is a matter of some controversy. In this publication, Alzheimer's disease refers to cases of early onset and to cases which occur after age 65.

The major debilitating symptoms of Alzheimer's disease include serious forgetfulness—particularly about recent events—and confusion. At first, the individual experiences only minor and almost imperceptible symptoms that are often attributed to emotional upsets or other physical illnesses. Gradually, however, the person becomes more forgetful and this may be reported by anxious relatives. The person may neglect to turn off the oven, may misplace things, may recheck to see if a task was done, may take longer to complete a chore that was previously routine, or may repeat already answered questions. As the disease progresses, memory loss and such changes in personality, mood, and behavior as confusion, irritability, restlessness, and agitation, are likely to appear. Judgment, concentration, orientation, writing, reading, speech, motor behavior, and naming of objects may also be affected. Even when a loving and caring family is available to give support, the victim of Alzheimer's disease is most likely to spend his or her last days in a nursing home or long-term care institution. At this time, there is no cure.

Biological Mechanisms

Glucose metabolism is one of three major interconnected measures of brain activity—the other two are brain blood flow and brain oxygen consumption. New noninvasive machinery which uses computer technology, allows simple tests of glucose metabolism and, in turn, provides a direct measure of activity in any given brain region. National Institutes of Health scientists and others using positron emission tomography (PET) and a compound similar in structure to glucose to measure glucose metabolism have come up with some fascinating findings about the workings of aged healthy and diseased brains.

Using PET to scan the normal aging brain, Stanley I. Rapoport, Ranjan Duara and their fellow scientists in the NIA Laboratory of Neurosciences have found no significant age-related alterations in brain glucose metabolism.[1] These investigators tested 40 men, aged 21 to 83, and found this was true for some several dozen regions of the brains that they scanned. These studies suggest that the healthy aged brain is as active and efficient as the healthy young brain. Of current interest to the investigators is why their findings are inconsistent with changes known to take place in the size and weight (i.e., the number of cells) of the brain as it ages, as well as findings of other investigators who have reported drops in glucose metabolism with age, and the controversial findings which suggest that brain blood flow and oxygen consumption may or may not change with age. Future studies by Rapoport and his colleagues will continue to build upon and analyze the results of this work. In the meantime, the investigators' findings are beginning to provide age-related normal values for glucose metabolism in the brains of healthy men of all ages.

PET scans are also beginning to show that various parts of the brain deteriorate at different rates as Alzheimer's disease progresses. NINCDS scientists Norman L. Foster, Thomas N. Chase and their associates have demonstrated that lowered metabolic rates in different parts of the brain can be linked to Alzheimer patients' inability to perform certain physical tasks.[2] The investigators selected 16 Alzheimer's patients who suffered from varying degrees of apraxia, a loss of voluntary movement without actual paralysis, and asked the patients to mimic, pantomime, or identify 75 body movements. Patients responded with varying success; different patients had different types of difficulties in performing tasks. On the basis of these and other preliminary test results, the investigators have suggested that Alzheimer patients with brain damage on the right side have difficulty mimicking or imitating actions, while those with damage on the left side are unable to follow verbal commands. According to Foster, other factors may affect how well a patient performs a task, including the complexity of the task and whether or not the action has a purpose. This may eventually help in clinical practice as physicians are better able to diagnose Alzheimer's disease and to treat patients.

Molecular Pathology

The changes most commonly associated with Alzheimer's disease occur in the proteins of the nerve cells of the cerebral cortex (outer layer of the brain) and lead to an accumulation of abnormal tangled fibers called neurofibrillary tangles. An important study of these characteristic nerve cell changes has revealed some unusual and unexpected findings. For several years, Dennis Selkoe, a neuropathologist and neurologist at the McLean Hospital in Belmont, Massachusetts, has received NIA grant support for his studies on the role and chemical composition of elements within normal and abnormal brain cells. Much of his work has focused on neurofilaments, elements within the cell that are made up of long hair-like strands of protein. In Alzheimer's disease, proteins like these bind together and twist into spiral-like configurations called paired helical filaments (PHF). Masses of PHFs form the characteristic neurofibrillary tangles of Alzheimer's disease. It is possible that these changes can be linked to cell death.

Selkoe and his colleagues have found that the proteins in Alzheimer tissue are highly resistant to standard protein solvents and that the molecules of the PHF's bind tightly together to form an extremely rigid "cross-linking" structure.[3] This is not the first time that cross-linking has been observed in aging human tissue. Other examples include the changes that take place in the formation of cataracts. In their most recent studies, Selkoe and his colleagues have compared the mechanisms responsible for cross-linkage in the lens of the aging eye to what may be going on in the aging brain. In the lens, a particular enzyme called transglutaminase appears responsible for the binding of protein. Selkoe has recently completed studies marking the presence of this enzyme in the human brain. Furthermore, the investigators have experimentally induced the development of a rigid molecular structure —although different in form from the PHF—by adding this enzyme to normal filaments. Future studies will expand the attempt to find out what causes the formation of structures that age and irreversibly alter brain cells, and play a major role in Alzheimer's disease.

With continued Federal support, Selkoe and his colleagues have developed what may become a definitive diagnostic test for Alzheimer's disease. In animal experiments, the investigators have developed an antibody which can selectively label the paired helical filaments which characterize Alzheimer's disease, and clearly distinguish these structures from normal brain proteins. Before Selkoe's pioneering work, studies had consistently suggested that virtually all proteins in Alzheimer tissue were similar to proteins in healthy aged brain tissue.

Because this new procedure entails surgical removal of a small section of the brain, the investigators caution that the current value of their work is somewhat limited. For the present time, their findings provide a powerful tool for studying the basic changes that take place in the brain as Alzheimer's disease progresses. Their findings might also help quickly identify Alzheimer's disease at autopsy. Before this work can proceed in living individuals, however, careful and sensitive attention must be given to the benefits and risks of brain biopsy in diagnosis.

The Search For a Cause

In a decade marked by major advances in the fields of neuroscience and aging research, scientists have employed a variety of methods to investigate the possible cause(s) of Alzheimer's disease. Studies have looked at the roles of deleterious changes in brain chemistry, trace metals, and slow-acting viruses, as well as the roles of heredity and of changes in the aging immune system.

Biochemical Studies

Since the first reports in the mid 1970's, research scientists have been studying evidence of a significant and progressive decrease in the activity of the enzyme choline acetyltransferase (ChAT) in the brain tissue of Alzheimer patients. ChAT is a crucial ingredient in the chemical process which produces acetylcholine, a neurotransmitter involved in both learning and memory. Until recently, the most exciting findings were those which showed a link between this change in neurochemical activity and changes in both cognition (such as memory loss and disorientation) and the physical appearance of Alzheimer brains, particularly the number of characteristic plaques (degenerated nerve cell pieces which form around a fibrous core in the cerebral cortex). In order to explore further the relationship between ChAT and Alzheimer's disease, scientists are using new techniques such as monoclonal antibodies to help map areas of the brain where ChAT is present. Other current studies are aimed at expanding our understanding of a host of chemicals in human aging and dementia.

Recent studies at the Johns Hopkins University bring us closer to understanding what causes this decline in the brain's complex chemical activity. In studying the brains of Alzheimer victims, NINCDS/NIA/NIMH grantees Donald Price and Joseph Coyle find a marked loss of nerve cells in a part of the base of the brain called the nucleus basalis.[4] Some patients with classical Alzheimer's disease have been shown to lose as many as 90 percent of these cells. Scientists are intrigued by the possibility of a link between this loss and the decrease in cholinergic activity: the nucleus basalis produces acetylcholine and utilizes the neurotransmitter and its enzymes in communicating with the brain's cortex via connecting pathways. It has been known for some time that aging produces a loss of cells in the brain's cortex. But NINCDS-supported investigations involving meticulous counting of nerve cells indicate that there is no major loss of cells in the brain's outer layer. Therefore, normal cell loss has never been able to explain the severe degree of cholinergic deficiency—between 75 and 95 percent—in this part of the Alzheimer brain. Since the loss of acetylcholine is so detrimental in Alzheimer patients, and the nucleus basalis now

appears to be one of the major sources of the substance, researchers hope to learn why nerve cells of the nucleus basalis seem to be selectively destroyed in Alzheimer's disease. Scientists are also interested in these findings because they indicate that brain centers innervating higher brain centers may be important in the development of Alzheimer's disease.

Trace Metal Studies

A new and controversial finding reported by scientists at the University of Vermont and the National Institute of Neurological and Communicative Disorders and Stroke has linked the results of two separate avenues of research on Alzheimer's disease—research that suggests that aluminum may contribute to the disease's development, and research that probes the excess incidence of dementia in three separate populations.

With grant support from the NIA, Daniel Perl of the University of Vermont has extended his earlier findings of accumulations of aluminum within the affected nerve cells of subjects showing the classic neurofibrillary tangles of Alzheimer's disease. In a collaborative study, Perl and NINCDS intramural scientists Gajdusek, Garruto, Yanagihara, and Gibbs reported high accumulations of aluminum, iron, and calcium in the brains of Chamorro natives of Guam who had died of amyotrophic lateral sclerosis (ALS) or parkinsonism-dementia.[1] This population is adversely affected by these two chronic disorders, both of which were previously suspected to be transmitted by a slow-acting virus. For several years, Gajdusek and his colleagues at the NINCDS have been studying the possible implications of Guam's environmental deficiency in calcium and magnesium and excess of aluminum and other metals.

Researchers in the field of aging have kept a watchful eye on studies in Guam because of the similarities between the parkinsonism-dementia syndrome and Alzheimer's disease. In both disorders, there is an excessive accumulation of neurofibrillary tangles in the brains of victims that is associated with severe dementia and death.

These latest findings by Perl, Gajdusek and colleagues reconfirm Perl's earlier work linking high concentrations of aluminum in the brain to the development of neurofibrillary tangles, as well as work of Japanese investigators in both Guam and Japan. NINCDS scientists are exploring the possibility that secondary hyperparathyroidism caused by lack of calcium and magnesium in the environment provokes an accumulation of metal ions within brain tissue.

Samples of garden soil and drinking water in Guam, as well as in parts of Japan and New Guinea that are similarly plagued by high incidences of ALS and dementia, indicate low levels of calcium and magnesium and unusually high levels of aluminum. All of these elements have similar chemical structures. Scientists have never been able to prove that aluminum alone predisposes a person to, or causes, Alzheimer's disease. It may be that high intake of aluminum over a long period of time, coupled with chronic low intake of vital minerals such as calcium and magnesium, ultimately results in a breakdown of the normal mechanisms which metabolize minerals. This, in turn, could result in what investigators find are toxic levels of these elements in the brain cells and in the walls of major blood vessels in the brain. Scientists have yet to determine how or why low intake of calcium and magnesium can lead to high levels of these elements in the brain but there appears to be a link since the same phenomenon occurs in three different high incidence areas. Perhaps the body is overcompensating for the lack of vital minerals by storing these in combination with other available trace elements in the bones. Ultimately this may lead to deposits in the central nervous system.

NIMH scientists are also involved in studies of how aluminum gains access to the brain. During the past several years, researchers at the NIMH Adult Psychiatry Branch at St. Elizabeths Hospital in Washington, D.C. have measured the concentrations of aluminum and a variety of other minerals in the hair of Alzheimer patients and their healthy spouses. Examples of these minerals are calcium, magnesium, manganese, copper, and zinc. To date, no difference in any of the minerals studied have been found between the two groups. Further, serum copper and zinc have been examined in both groups. Again, no differences have been noted.

Future studies in this area will determine whether accumulations of metals in the brain are a primary cause of Alzheimer's disease or if other factors or circumstances might combine with environmental factors to trigger the onset of chronic, but ultimately fatal, diseases of the nervous system.

Slow Virus Studies

The quest for an understanding of what causes Alzheimer's disease continues with studies on central nervous system (CNS) diseases believed to be caused by slow-acting transmissible viruses.

Scrapie, a CNS disease that affects sheep, has provided a model for the study of dementing disorders in humans, including Alzheimer's disease. It is difficult to find an animal model for Alzheimer's disease, since dementia involves the loss of a capacity we cannot be sure animals ever had. Nonetheless, scientists are actively pursuing an animal or other model. Scrapie is similar to kuru and Creutzfeldt-Jakob disease, two rare diseases which cause progressive, irreversible dementia in humans. This fact, plus the well-established evidence that scrapie is the result of a slow-acting infectious agent, encouraged a new avenue of research on the possible causes of CNS disease in humans.

Scientists pursuing this line of research, however, have consistently failed in their efforts to identify and isolate any component of the infectious agent. Research at the University of California at San Francisco suggests that a protein is the vital force of the scrapie agent. NIA/NINCDS grantee Stanley B. Prusiner finds that animals with scrapie are infected by what he calls a small proteinaceous infectious particle, or "prion."[6] Prusiner's latest research tentatively suggests that the amyloid plaques seen in victims of Creutzfeldt-Jakob disease and kuru, two transmissible degenerative brain diseases, may be composed of prions. Amyloid plaques are also present in the Alzheimer brain.

Prions have many properties which distinguish them from typical viruses. Although viruses contain nucleic acids which carry all of the information necessary for the virus to multiply and spread infection, prions may or may not contain a nucleic acid. Since nucleic acids are necessary for proteins to replicate, this raises some exciting questions.

Prusiner's work remains to be confirmed, but if it is, it might significantly alter our understanding of the nature of this virus and how it works with possible implications for CNS degenerative disorders such as Alzheimer's disease.

Related Research

The National Institute of Allergy and Infectious Diseases (NIAID) conducts research on the biology and epidemiology of viruses associated with persistent and latent infections. William J. Hadlow and his colleagues at the NIAID Rocky Mountain Laboratories have studied Suffolk sheep naturally infected with scrapie virus and have outlined the main events in the infectious process. They found the virus in such lymphatic tissues as tonsils and in the intestines of clinically normal lambs, aged 10 to 14 months, whose mothers later developed the symptoms of scrapie. As the lambs grew older, virus was found in the brains and spinal cords. These findings suggest that primary infection occurs by way of the digestive tract, either before birth from virus in amniotic fluid or after birth from virus in a contaminated environment.

Hadlow's study on scrapie may have implications for Creutzfeldt-Jakob disease, providing clues not only to its cause and development, but also to its possible links with exposure to the scrapie virus. For example, many investigators have looked for some association with eating sheep brain. But this study shows that virus is not present in the brains of young lambs, those most often used for human food, and underscores the importance of further research.

Since the central nervous system is susceptible to viral infections, research on these diseases may eventually provide a key to understanding currently baffling degenerative diseases such as Alzheimer's disease.

Immunological Studies

NINCDS-supported investigators at Sloan-Kettering Institute for Cancer Research are exploring the relationship between changes in the immune system and central nervous system disease. Research in patients who have a specific immune system deficiency has linked dietary intake to immune mechanisms. Previous studies have examined this relationship in cardiovascular disease. Investigators are now attempting to elucidate immunologic mechanisms in such chronic degenerative disorders as Alzheimer's disease.

Genetic Studies

For several decades, research on Alzheimer's disease has hinted that in either its early onset or senile form, the disease might be hereditary. In what amounts to a handful of studies on genetic influence, researchers have found an increased incidence of some form of dementia among parents and siblings of victims. Some studies show a slight increase; others show a considerable one over the occurrence of dementia in the general population. One researcher has suggested that early onset Alzheimer's disease poses a greater risk to relatives than late onset disease. Practically no data are available on risk to children. Briefly stated, the studies show a clustering of dementia cases in some families but no consistent pattern of genetic transmission.

Genetic research may eventually tell us whether we are dealing with one disease or more in the presenile and senile forms of Alzheimer's disease. Such studies may also provide a way to diagnose dementia accurately using a "marker" for the disease. At the Brentwood VA Medical Center and the UCLA School of Medicine, Lissy Jarvik and her colleagues have found something unusual in the behavior of white blood cells taken from patients with Alzheimer's disease.[7] With support from NIMH, Jarvik plans to continue to study what she describes as the "disoriented" behavior of cells from Alzheimer patients when exposed to temperatures which generally elicit a specific response from cells from healthy individuals. Future research from this laboratory will attempt to determine if this change is consistent and what causes it.

Little research has so far addressed whether psychosocial factors (e.g., environmental stressors, depressive states, alcoholism) might contribute to the cause or development of Alzheimer's disease. To date, behavioral science research has focused mainly on the search for definitive diagnostic tests, including tests which will differentiate between Alzheimer's disease and multi-infarct (vascular) dementia; on changes in language use in relation to brain function and dysfunction; and on special supports needed by families of victims.

Language Usage

General difficulties in language usage and comprehension have always been included among the symptoms of Alzheimer's disease and other irreversible dementias. Now, an NIA-supported research scientist finds that specific language problems might be used to detect and diagnose various forms of dementia.

The recommended examination of an older person complaining of memory loss and confusion includes a battery of physical and neurological tests as well as certain psychological tests to detect or monitor declining skills. Commonly used tests can quickly evaluate a person's sense of time, place, and self. They can also assess short-term memory as well as the person's ability to complete simple mathematical calculations, both of which are among the first clinical signs of Alzheimer's disease. More and more, however, mental status tests include questions aimed at evaluating language skills. A patient will be asked to name objects, exhibit comprehension of a spoken or written statement, or write a spontaneous sentence.

Kathryn Bayles, an NIA grantee at the University of Arizona, has found that asking subjects to name common household or everyday objects—such as a broom, a purse, an apple, or a telephone—can easily differentiate between moderately impaired Alzheimer patients and healthy older individuals, and in some cases can detect mild cases of Alzheimer's disease.[8] Such demands can uncover the subtle, if serious, deficiencies often masked by the residual social skills of an Alzheimer patient in early and middle stages of the disease.

Bayles' study is one of several looking at the language skills of healthy aged adults and what happens to these skills when subjects suffer from Alzheimer's disease, Huntington's disease, Parkinson's disease, or multi-infarct dementia. Her results confirm that patients in all stages of dementia have difficulties expressing themselves, but also suggest that tests of language skills are sometimes more sensitive than certain psychological tests to the presence of dementia. Although her studies are not yet completed, it appears that the deterioration of language skills is more severe and more rapid in Alzheimer's disease than in other forms of irreversible dementia.

As this study progresses, Bayles and her colleagues hope to develop a standard against which health professionals can measure the verbal performance of their patients. According to Bayles, tests of linguistic skills might be refined to determine the presence and severity of senile dementia and to outline interventions that might improve comprehension. She has already found a certain logic in the incorrect responses given by Alzheimer patients: moderately affected patients who cannot name a given object often will substitute a word which describes the object or the name of a similar object. At the very least, such studies might provide valuable information on the best methods for communicating with patients over the course of a disease which progressively limits communication.

Diagnosis of Alzheimer's Disease

What happens when an older person starts to show signs of "senility"? With luck, someone—perhaps a relative—will realize the importance of going to a physician to find out what is causing the problem, if it is curable and, if it is not, what can be done to help. The victim's first contact with a health professional is likely to be an internist, a geriatrician, or a general practitioner. Because of the variety of conditions that can cause what is medically known as senile dementia—and also because of the wide range of symptoms—the patient may eventually consult or be examined by a neurologist, a psychiatrist, a psychologist, a radiologist, and/or a social worker. In this way, the family might be exposed to the terminologies used by various specialists: senile dementia, Alzheimer's disease, organic brain syndrome, brain failure, and senile psychosis. The accurate diagnosis of "senility," by whatever name, is clearly a challenge for physicians.

According to a study at the Philadelphia Geriatric Center, professionals from different clinical disciplines generally agree in the diagnosis of senile dementia. NIA grantee Samuel Granick has found that despite their dependence on the tools of their individual specialties, almost all of the clinicians involved in his research felt that severe memory loss, disorientation, and a decline in mental functions are the most distinctive symptoms of senile dementia. The physicians conducted extensive medical, social, and behavioral evaluations of 111 elderly volunteers.

As part of their research, Granick and his colleagues also developed a list of 141 medical and psychological factors which can be used to detect senile dementia in its earliest stages. This list included a few purely medical variables, such as a history of heart problems, which, according to the investigators, might distinguish individuals with moderate to severe forms of dementia from nondemented subjects if vascular dementia is the cause. None of these medical factors were sensitive enough to detect mild forms of dementia. On the other hand, tests which measured aspects of psychological function showed the extensive and seriously deteriorative effects of senile dementia. Combining tests even made it possible to single out patients who were only mildly affected. According to Granick, performance on behavioral or psychological tests would appear to be more useful than the standard medical measures currently used in the diagnosis of senile dementia.

Granick further refined his list of factors and came up with 15 variables—most of which deal with the quality of intellectual function—which together can serve as a basis for diagnosis. Using a step-by-step process to measure such functions as mental status and memory, Granick accurately classified 93 percent of a smaller group of volunteers in the study as either mildly demented, suffering from moderate to severe dementia, or nondemented. Since there has never been a single reliable and valid test to diagnose senile dementia in its earliest stages, such work by behavioral scientists may someday prove extremely useful to physicians.

Family Studies

In addition to studying the mechanisms and cause(s) of Alzheimer's disease, research scientists have begun to take a closer look at the families of Alzheimer victims. Alternately parallelling, inspiring, and building upon the development of family support groups, these studies have uncovered some intriguing findings about how families cope and how to help them cope.

With support from NIMH, Steven Zarit of the University of Southern California will build upon earlier research on strategies for coping. Zarit and his colleagues have found that health professionals can greatly reduce the amount of stress that impedes a caregiver's ability to function by 1) providing information about the disease, 2) offering alternative solutions for day-to-day problems, and 3) providing an atmosphere whereby relatives, friends, or other caregivers can offer much-needed support.[9] According to the investigators, it is important —but rarely the case—that health professionals take the time to answer the many questions relatives will ask about the causes of the illness, medical treatments that may or may not be helpful or harmful, and what the illness will do to the patient's behavior. Such information is critical to developing reasonable solutions to practical problems the patient may have with eating, sleeping, and other routine behaviors. It is also important to offer caregivers individual or family counseling or to provide a structured environment in which they can discuss their experiences and solutions with others in the same situations. In the end, say the investigators, it is the ability of the caregiver to develop and/or maintain good coping skills, and to be able to count on support from family and friends, which will determine his or her ability to continue providing care, regardless of the severity of the dementia.

At the University of Michigan, Dorothy Coons and her colleagues have obtained private funding from the American Association of Retired Persons to quantify further the experiences of families. The investigators developed and distributed a questionnaire to 510 families of Alzheimer victims. Of the 75 percent who returned completed questionnaires, most were caring for relatives at home. Of those who had placed a relative in a long-term care institution, most had maintained the patient at home for as long as possible.

In what amounted to a tremendous outpouring of information, the responses told of the frustrations of obtaining a diagnosis, of patients losing jobs and, oftentimes, benefits before a diagnosis was established, of the guilt which tore families apart when certain decisions were made, and of victims as well as caregivers fighting off alcoholism and depression. The investigators also found evidence of a wide variety of successful coping strategies: in some cases, those who responded felt the disease had acted as a catalyst in uniting the family; in other cases, family members became educators and advocates on behalf of patients. Once again, a major area of concern was the need for more information and emotional support from health professionals and others.

There is a serious need for further research on the experiences and needs of families of Alzheimer patients. As the primary source of care for those who suffer from dementia, the family bears most of the economic and emotional burden of the disease which might otherwise fall on social institutions. Moreover, research is needed on the possible contributions of family reactions to the course of the disease in the patient.

Clinical Research

A number of scientists, including clinicians, gerontologists, biochemists, neuropathologists, neurophysiologists, psychologists, mathematicians, and many others, are employing the early findings of biomedical, social, and psychological studies to design clinical research projects—in particular, studies aimed at improving diagnosis, some of which were highlighted above, and studies aimed at improving treatment.

Sleep Studies

At the University of Washington, investigators receiving support from the NIMH, NIA, and the Veterans Administration are attempting to determine if the sleep and wake patterns of older individuals can be used to detect the presence and monitor the progress of Alzheimer's disease. In a series of sleep laboratory experiments, Patricia Prinz and her colleagues have looked at healthy young and old subjects and at patients with a diagnosis of Alzheimer's disease. Her findings in older healthy adults confirm early work on "normal" sleep patterns in the elderly: older people experience less of certain "stages" of sleep and awaken more frequently throughout the night than healthy young adults. She also found, however, that these and other changes were significantly more pronounced in Alzheimer patients, including frequent awakenings. The more advanced the disease, the more severe the changes.[10]

In her more recent studies, Prinz finds that impaired sleep is evident even in the very early stages of Alzheimer's disease and that the changes which occur are striking enough to differentiate healthy subjects from patients with severe, moderate, or even mild cases of the disease. In the next part of her investigation, Prinz will examine the sleep/wake patterns of elderly individuals who have complaints of memory loss to see if she has indeed found a "marker" to detect early cases of Alzheimer's disease.

Treatment Approaches

As noted above, one of the most consistent changes in Alzheimer's disease involves a decrease in the activity of the chemicals collectively comprising the brain's cholinergic system. While recognizing that Alzheimer's disease probably involves more than one neurotransmitter, basic scientists have attempted to determine what causes this particular decline and clinical scientists have attempted to compensate for this deficit as a way of treating the serious symptoms of Alzheimer's disease.

The first studies in this area involved ingestion of the drug choline chloride, which not only produced some rather unpleasant side effects, but failed to increase acetylcholine production in the brain. Other early studies employed pure forms of lecithin, the dietary source of choline with the same intent of increasing acetylcholine production. Lecithin increased the level of choline in the blood more than choline chloride, continued to have this effect for a longer period of time, and had no serious side effects—but also showed no consistent or marked benefit.

In 1978, research at the Bronx VA Hospital suggested that physostigmine, a drug which blocks the otherwise fast breakdown of acetylcholine in the brain, had a positive effect on the memory of elderly Alzheimer patients, but that the dose required to do so varied from subject to subject." Use of the drug, however, was plagued by problems. It was not practical for Alzheimer patients since it had to be given by injection and its effects lasted less than one hour. Now, a research team supported by the NIA and the NINCDS at the Albert Einstein College of Medicine may have overcome some of the difficulties inherent in the use of this drug. Using an oral form of physostigmine, Leon Thal found marked improvement in six out of eight Alzheimer patients when the drug dose was carefully planned for each individual and given in combination with lecithin. The drug's effect lasted longer than the investigators anticipated so that memory improvement was still noticeable on the morning after the drug was administered. Also, side effects such as nausea and cramps were only apparent when the patient received more than the optimal dose to improve his/her memory. With support from the NIA, Thal hopes to expand these studies and to begin work on tetrahydroaminoacridine, a drug which also acts to slow breakdown of acetylcholine but may be safer and more effective than physostigmine.

At the Burke Rehabilitation Center in White Plains, New York, scientists are studying yet another approach to treatment of Alzheimer's disease. It is known that a variety of normal functions, critical to the life of brain cells, are controlled by calcium. Typically, calcium concentrations in the cell are maintained at a very low level, increasing only when the cell is stimulated and prepared to release neurotransmitters to other cells or other parts of the cell. At this point, it becomes crucial for calcium concentrations to increase temporarily.

Several studies of the aging brain have suggested that calcium activity decreases with aging, possibly compromising cell communications. This is an interesting finding when coupled with the knowledge that acetylcholine is one of several neurotransmitters partially influenced by calcium.

NIA-supported investigator Gary Gibson is building upon these earlier findings in an attempt to stimulate calcium concentrations and increase the synthesis and release of acetylcholine. Gibson and his colleagues have discovered a close link between the drop in synthesis and release of acetylcholine in healthy aged rats. These decreases are not as dramatic as those seen in Alzheimer's disease, and do not result in the general decrease in acetylcholine levels that is typical of Alzheimer's, but are nonetheless connected with certain learning and memory problems in animal studies. Since both synthesis and release of the neurotransmitter are dependent upon calcium concentrations, the investigators injected the rats with a drug which stimulated oxygen metabolism, increased calcium concentrations, and, in turn, improved old rats' performance on certain tests which involved learning.

While some investigators have attempted to increase acetylcholine synthesis indiscriminately in all cholinergic cells, and others are trying to prevent the otherwise fast breakdown of acetylcholine once it is synthesized, Gibson and his colleagues are trying to increase the ability of the cell to produce acetylcholine only when it is needed. These investigators have found a means to selectively pinpoint the sites at which the neurotransmitter is released and to program its release when the cell is active. Such an approach may ultimately benefit Alzheimer patients by allowing treatment with a minimum of side effects.

Intramural Initiatives

The NIA Laboratory of Neurosciences (LNS) clinical program, established in 1980, is involved in an intensive investigation of brain metabolism in relation to normal human aging and dementia. In September 1982, Stanley I. Rapoport, LNS chief, and Neal R. Cutler, chief of the LNS clinical program, together with a staff of research neurologists, psychologists, and other health professionals admitted the program's first inpatients thus initiating a series of activities focusing primarily on the dementias and related neuropathological diseases of the elderly. Studies look closely at Alzheimer's disease and at multi-infarct dementia, which is caused by a series of minor strokes.

These studies of dementia are set in the context of a clinical program which examines the normal aging process from biochemical, cardiovascular, and general physiologic perspectives, including careful evaluation of brain function. The primary clinical goals of the program are 1) to develop a clear picture of brain physiology in normal aging and age-related disease; 2) to evaluate the changing pharmacokinetics and pharmacodynamics of various antihypertensives and central nervous system agents in the elderly; 3) to develop a better understanding of the causes, courses, and treatments of different forms of dementia; and 4) to encourage other NIH components to focus their clinical studies on the growing aging population.

Rapoport and his staff hope to use the results of their work to eventually design pharmacological approaches to treat reversible cognitive defects of aging and irreversible dementia and to understand better the neurochemical changes that occur in Alzheimer's disease.

The principal research efforts of Thomas N. Chase and the NINCDS intramural staff are directed towards the rational development of improved drug treatments for nervous system disease. Of particular interest are the investigators' attempts, using human subjects as well as animal models, to relate the activity of particular neurotransmitter systems such as the dopamine system, to specific brain functions. New drugs are then evaluated in animal models and in man for their ability to selectively modify these systems and thus ameliorate debilitating neurologic or psychiatric changes.

In one of several studies on senile dementia, NIMH scientists are continuing their investigations of neurofibrillary tangles in Alzheimer's disease. For some time, it has intrigued these investigators that nerve cells with neurofibrillary degeneration may be functionally impaired, but do not seem to rapidly deteriorate and die. If aluminum is, in fact, responsible for some of the degenerative brain changes in Alzheimer's disease, then attempts to remove this metal from the human body could have significant effects on the course of the illness. Following the lead of Czechoslovakian investigators who have suggested that aluminum interacts with fluoride ions and is in this way excreted from the body, scientists at the NIMH Adult Psychiatry Branch are now conducting a long-term study of the effects of sodium fluoride on the course and outcome of Alzheimer's disease. Results in the first patients studied are sufficiently encouraging to warrant continuation of this project. David Shore and Richard Wyatt expect to complete this pilot study during the fall of 1984.

Over the past decade, research scientists have made major advances in their studies of aging and the brain. At the same time, scientists, health professionals, policymakers, and the public have experienced a growing awareness of the impact of Alzheimer's disease.

Since 1976, Alzheimer's disease has become a major priority for Federally-supported scientific research. Scientific studies of the diagnosis, causes, nature, incidence, prevalence, and course of Alzheimer's disease have established a solid foundation for research on the care, and possible treatment of its victims. At some future date, we may be able to cure or even prevent Alzheimer's disease. Much of this is due to the increased interest and growing cooperation among the Federal research agencies responsible for studies on aging, neurological disorders, and mental health.

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Appendix: Total Obligations for SDAT and Related Disorders (Dollars in Thousands)

Institute	*1976*	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*	*1984 (est.)*
NIA	857	1500	1960	4142	4211	5196	8054	11848	18480
NIMH	728	815	790	1315	2151	4700	4800	5000	5600
NINCDS	2314	2333	2422	2844	4960	5427	6243	8678	10924
NIAID	—	—	—	1381	1775	1394	1256	1041	1435
Total	3899	4648	5172	9682	13097	16717	20353	26567	36439

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402

*U.S. GOVERNMENT PRINTING OFFICE: 1984-439-889

National Institute on Aging
NIH Publication No. 84-2500
July 1984